

The Togetherness of PQ (Programming & Quality) *- A hand-in-hand affair*

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Agenda

- *Importance of First Time Right (FTR)*
- *Current quality control procedure in CRO's*
- *Challenges in achieving FTR*
- *Solutions to overcome these challenges*
- *Measure, Analyse and improve*
- *Importance of technology*

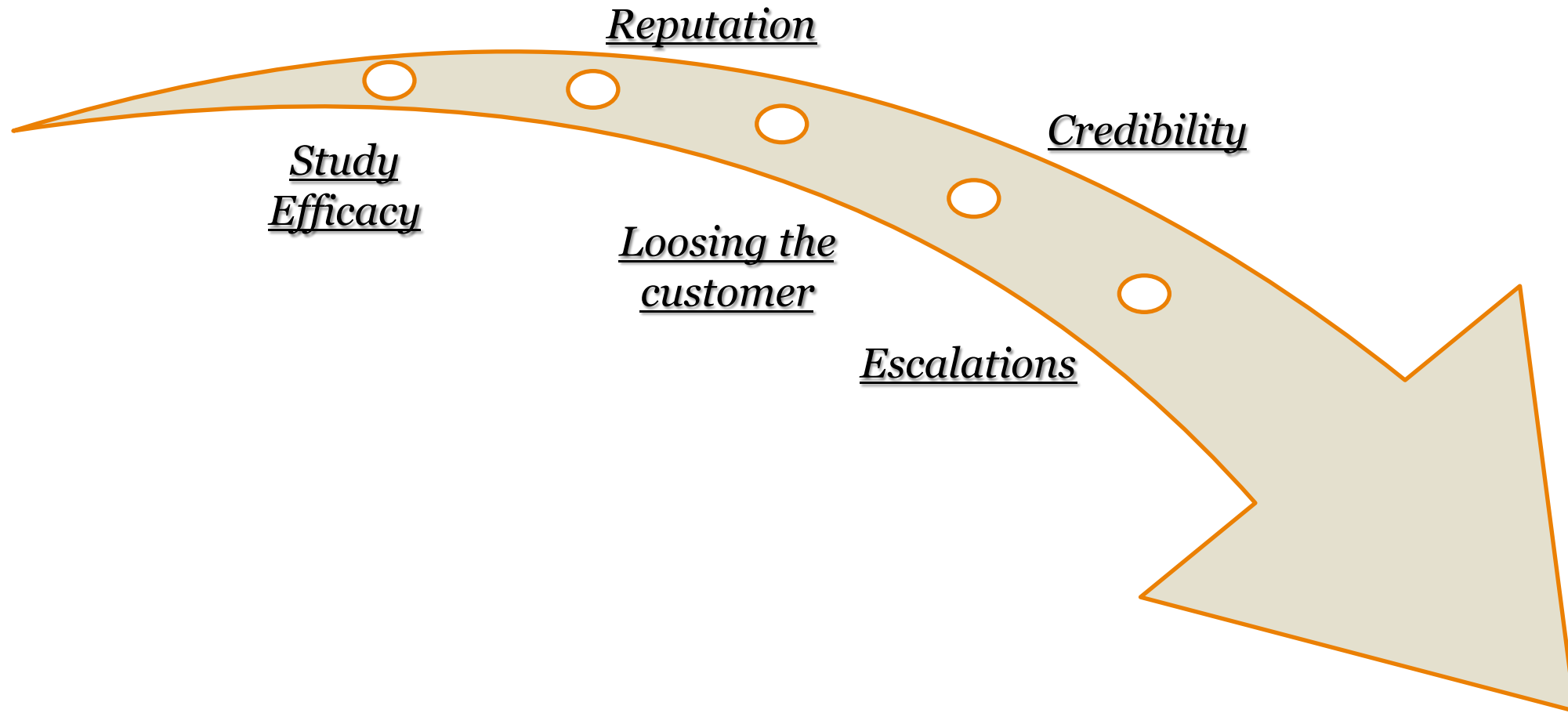
Importance of First time Right

- *Cost Factor*
- *Human Factor*
- *Accuracy Factor*
- *Time Factor*

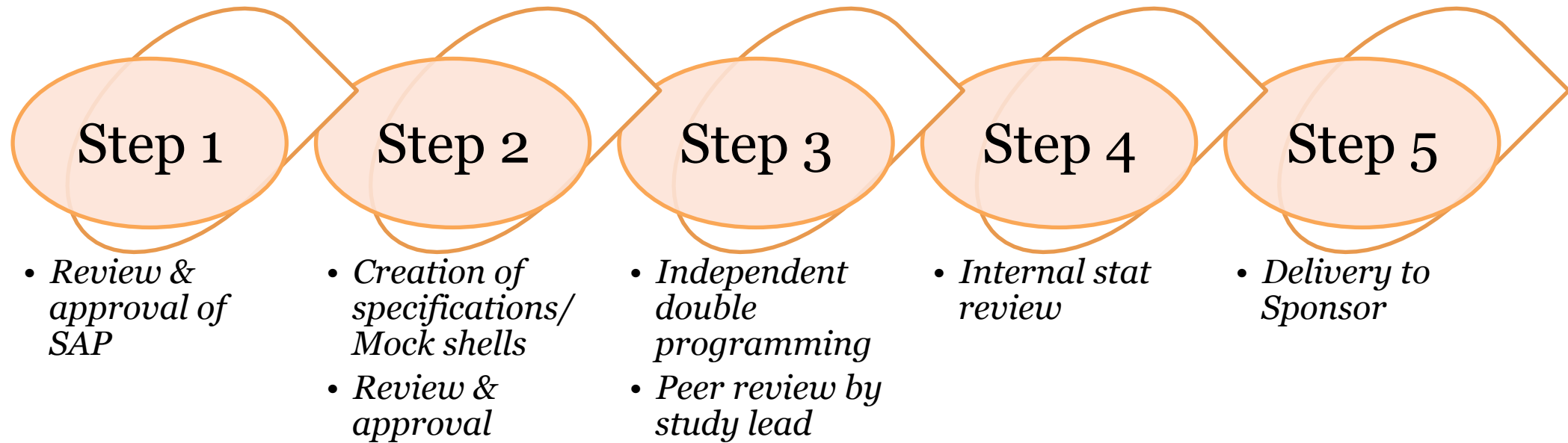


Downstream effects of MTW

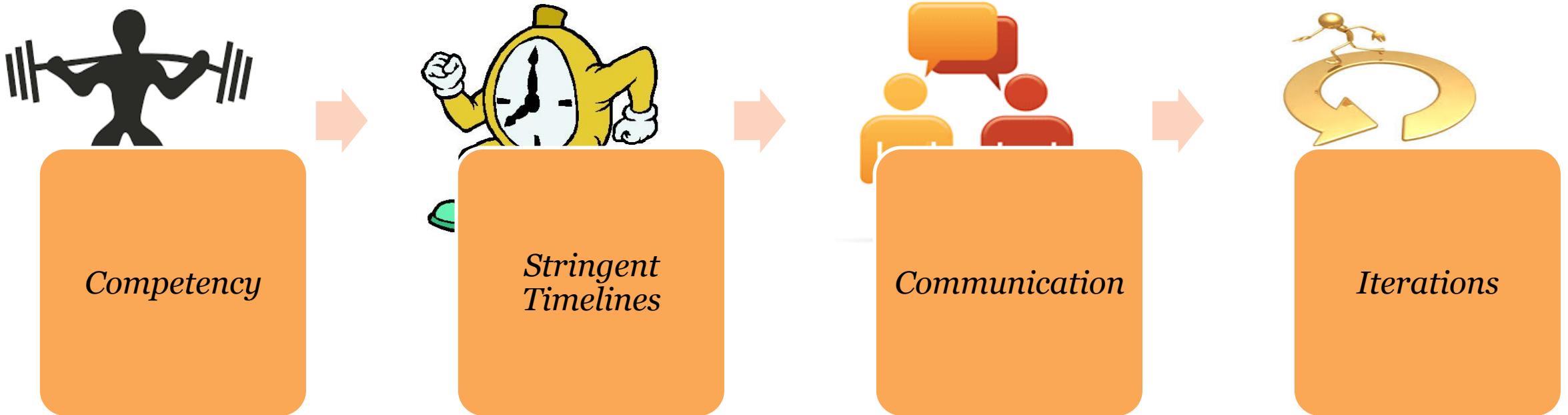
(Multiple times wrong)



Current practice in CRO's



Challenges in achieving FTR



Checklist for Datasets

- *Dataset and variable labels match the specifications*
- *Completeness/appropriateness of variables in ADAM/Analysis dataset w.r.t mock*
- *Sort order for final dataset*
- *Duplicate records*
- *Display order of variables in the dataset*
- *Opencdisc validator (now pinnacle 21)*

Opencdisc Report Sample

DOMAIN ABBR., LABEL AND CLASS AS PER IG

INPUT DATASET DETAILS

OBSERVATIONS NOT
CONSIDERED FOR ANALYSIS -
REJECTS
ERRORS - WHICH ARE NOT
ALLOWED AS PER IG
WARNING - WHICH ARE NOT
PRESENT/PERMISSIBLE AS PER IG

Processed Sources								
Domain	Label	Class	Source	Records	Rejects	Errors	Warnings	Notices
GLOBAL	Global Metadata	--	--	--	0	1	6	0
AE	Adverse Events	EVENTS	AE.xpt	271	0	25	577	7
CE	Clinical Events	EVENTS	CE.xpt	1	0	8	2	4
CM	Concomitant Medications	INTERVENTIONS	CM.xpt	3271	0	89	2698	0
DM	Demographics	SPECIAL PURPOSE	DM.xpt	366	0	49	86	11
EX	Exposure	INTERVENTIONS	EX.xpt	1548	0	10	1550	1
FA	Findings About Events or Interventions	FINDINGS	FA.xpt	2536	0	1416	1406	1
RELREC	Related Records	RELATIONSHIP	RELREC.xpt	12	0	5	0	0
SC	Subject Characteristics	FINDINGS	SC.xpt	1390	0	9	2786	0
SUPPAE	Supplemental Qualifiers [AE]	RELATIONSHIP	SUPPAE.xpt	276	0	7	0	0
SUPPCM	Supplemental Qualifiers	RELATIONSHIP	SUPPCM.xpt	3058	0	8	0	0
SUPPDM	Supplemental Qualifiers [DM]	RELATIONSHIP	SUPPDM.xpt	796	0	5	0	0
SV	Subject Visits	SPECIAL PURPOSE	SV.xpt	1798	0	4	27	0
Total				15323	0	1636	9138	24

Opencdisc Report Sample

DOMAIN
ABBR AS
PER IG

OBS AS
PER XPT
PROV

VARIABLE
NAME AS
PER IG

VALUES
AS PER
XPT

RULE REF
AS PER IG
INTEGRATED
IN PINNACLE

DESCRIPTION OF ISSUE

Domain	Record	Count	Variables	Values	Pinnacle 21	Publisher I	Message	Category	Severity
AE			VARIABLE, DATASET	EPOCH, AE	SD1077	FDAC021	FDA Expected variable EPOCH not found	Metadata	Warning
AE	11		AEDECOD	null	SD0002	FDAC018	NULL value in AEDECOD variable marked as Required	Presence	Error
AE	21		AEDECOD	null	SD0002	FDAC018	NULL value in AEDECOD variable marked as Required	Presence	Error
AE	83		AEDECOD	null	SD0002	FDAC018	NULL value in AEDECOD variable marked as Required	Presence	Error
AE	95		AEDECOD	null	SD0002	FDAC018	NULL value in AEDECOD variable marked as Required	Presence	Error
AE	121		AEDECOD	null	SD0002	FDAC018	NULL value in AEDECOD variable marked as Required	Presence	Error
AE	122		AEDECOD	null	SD0002	FDAC018	NULL value in AEDECOD variable marked as Required	Presence	Error
AE	217		AEDECOD	null	SD0002	FDAC018	NULL value in AEDECOD variable marked as Required	Presence	Error
AE	235		AEDECOD	null	SD0002	FDAC018	NULL value in AEDECOD variable marked as Required	Presence	Error
AE	247		AEDECOD	null	SD0002	FDAC018	NULL value in AEDECOD variable marked as Required	Presence	Error

Category of checks

<i>Category</i>	<i>Severity</i>
Consistency	Error
Cross-reference	Warning
Format	Notices
Limit	
Metadata	
Presence	
Terminology	

Few checks done by opencdisc

- *NULL value in -- variable marked as Required*
- *Duplicate value for --SEQ variable*
- *Missing value for --STRESC, when --DRVFL='Y'*
- *--STDTC is after --ENDTC*
- *Missing value for --ORRESU, when --ORRES is provided*
- *Subject is not present in DM domain*
- *Consistency of ARm, EPOCH, VISIT across domains*

Checklist for Tables

Cosmetic Checks

- *Font size for the body as well as header and footer*
- *Content of titles and footnotes*
- *Rounding of decimals as per mock*
- *Page overflows*
- *All abbreviations displayed in footer*

Logical Checks

- *Mean & Median values lying within the range*
- *Percentage > 100 in count tables*
- *Consistency between units & values*
- *Population definition as per mock*
- *Counts & numbers cross checked with listings & dataset*

Sample lab table

Table 14.3.3
Summary of Change from Pre-Dose in Labs
Safety Population

Parameter	Visit/Timepoint Statistic	At Timepoint	Change from Pre-Dose	At Timepoint	Change from Pre-Dose	At Timepoint
Creatine Kinase [U/L]	n	8	16	6	8	.
	Mean	98.6	84.6	107.5	-55.0	.
	SD	46.19	24.21	36.97	53.44	.
	Min	59	52	60	-172	.
	Median	62.5	79.5	104.5	-39.5	.
	Max	195	129	170	-5	.
	24H					
	n	8	16	6	8	.
	Mean	80.3	74.6	83.0	-73.4	.
	SD	27.98	20.32	19.68	72.85	.
Creatine Kinase [IU/L]	Baseline					
	n	.	3	.	.	6
	Mean	.	217.0	.	.	128.2
	SD	.	47.13	.	.	34.01
	Min	.	172	.	.	67

Note: Pre-dose is defined as the last non-missing measurement prior to the study drug administration in each treatment.
Only subjects with both a pre-dose value and a timepoint value are summarized at a given timepoint.

SAME PARAMETER WITH
DIFFERENT UNITS

Cross Checking between tables

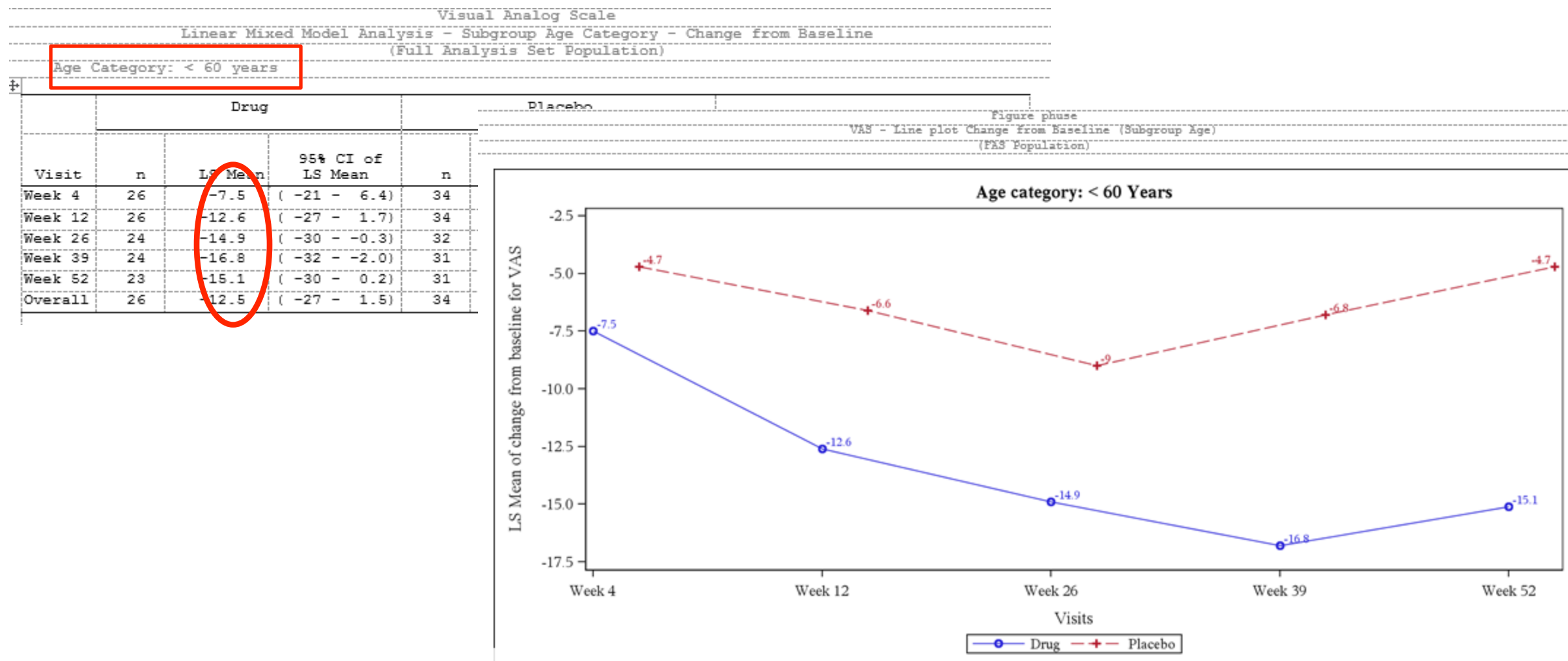
Overall AE Table

with one or more adverse events	79 (62.7)	67 (53.2)
with no adverse events	47 (37.3)	59 (46.8)
with one or more treatment emergent adverse events	63 (50.0)	55 (43.7)
with treatment related treatment emergent adverse events	18 (14.3)	21 (16.7)
with serious adverse events	11 (8.7)	6 (4.8)
with treatment related serious adverse events	2 (1.6)	1 (0.8)
who died	0 (0.0)	0 (0.0)
discontinued treatment due to an adverse event	32 (25.4)	9 (7.1)
discontinued treatment due to a treatment related adverse event	6 (4.8)	3 (2.4)
discontinued treatment due to a serious adverse event	7 (5.6)	2 (1.6)
discontinued treatment due to a treatment related serious adverse event	1 (0.8)	0 (0.0)

Serious adverse events by preferred term

Preferred Term	n (%)	n (%)
Subjects with at least one serious adverse event	11 (8.7)	6 (4.8)
Bipolar I disorder	5 (4.0)	1 (0.8)
Mania	1 (0.8)	1 (0.8)
Cholecystitis chronic	0 (0.0)	1 (0.8)
Convulsion	0 (0.0)	1 (0.8)
Depression	0 (0.0)	1 (0.8)

Cross checking between tables and figures



Checklist for Listings

Cosmetic Check

- ✓ *Truncation of text (eg. AE Description, Laboratory comments)*
- ✓ *Column labels as per mock*
- ✓ *Rounding of decimals as per mock*
- ✓ *All abbreviations displayed in footer*
- ✓ *Alignment of variables*
- ✓ *Cosmetics like Spell checks, sort order, page break*

Logical Check

- ✓ *Population used as per mock*
- ✓ *Proper sub setting flags and conditions*

Checklist for Figures



Cosmetic Check

- *X-axis and Y-axis scales*
- *Colour code of lines if applicable*
- *Legends are displayed properly*
- *All abbreviations displayed in footer*

Logical Check

- *Cross check numbers with tables (if applicable)*

Good programming practices

- *Naming convention of datasets and TFL's*
- *Header information*
- *Modification history and comments in your programs*
- *Dynamic coding to handle data updates*
- *Centrally controlled titles and footnotes*
- *Clean logs (No Errors, Warnings and some Notes)*

Example of defensive coding

Table 10-3-1 Summary of Demographic Data for Open-Label Subjects (All Subjects Treated from the Open-Label Treatment Period)

	Total N=xxx
Sex (n, %)	
Male	xx (xx.x)
Female	xx (xx.x)
Race (n, %)	
White	xx (xx.x)
Non-White	xx (xx.x)
Black or African American	xx (xx.x)
Asian	xx (xx.x)
American Indian or Alaskan Native	xx (xx.x)
Native Hawaiian or Other Pacific Islander	xx (xx.x)
Multiracial	xx (xx.x)
Race (n, %)	
White	xx (xx.x)
Black or African American	xx (xx.x)
Others	xx (xx.x)
Ethnicity (n, %)	
Hispanic Or Latino	xx (xx.x)
Not Hispanic Or Latino	xx (xx.x)
Age (years)	
Mean (SD)	xx.x (xx.x)
Median	xx.x
Range	xx - xx
Age (years) (n, %)	
18 - 64 years	xx (xx.x)
≥ 65 years	xx (xx.x)
Region (n, %)	
US	xx (xx.x)
Non-US	xx (xx.x)

Tips for defensive coding

- When coding IF-THEN-ELSE constructs use a final else statement to trap any observations that do not meet the conditions in the IF-THEN clauses.

```
Data vs1;  
  set vs;  
  ady= adt - trtsdt ;  
  if . < ady <= 7 then avisitn = 1 ;  
  else if 8 < ady <= 14 then avisitn = 2 ;  
  else if 15 < ady <= 21 then avisitn = 3 ;  
  else if 22 < ady <= 28 then avisitn = 4 ;  
  else put 'WARNING: out of window records: ' usbjid = ady= adt = trtsdt = ;  
run;
```

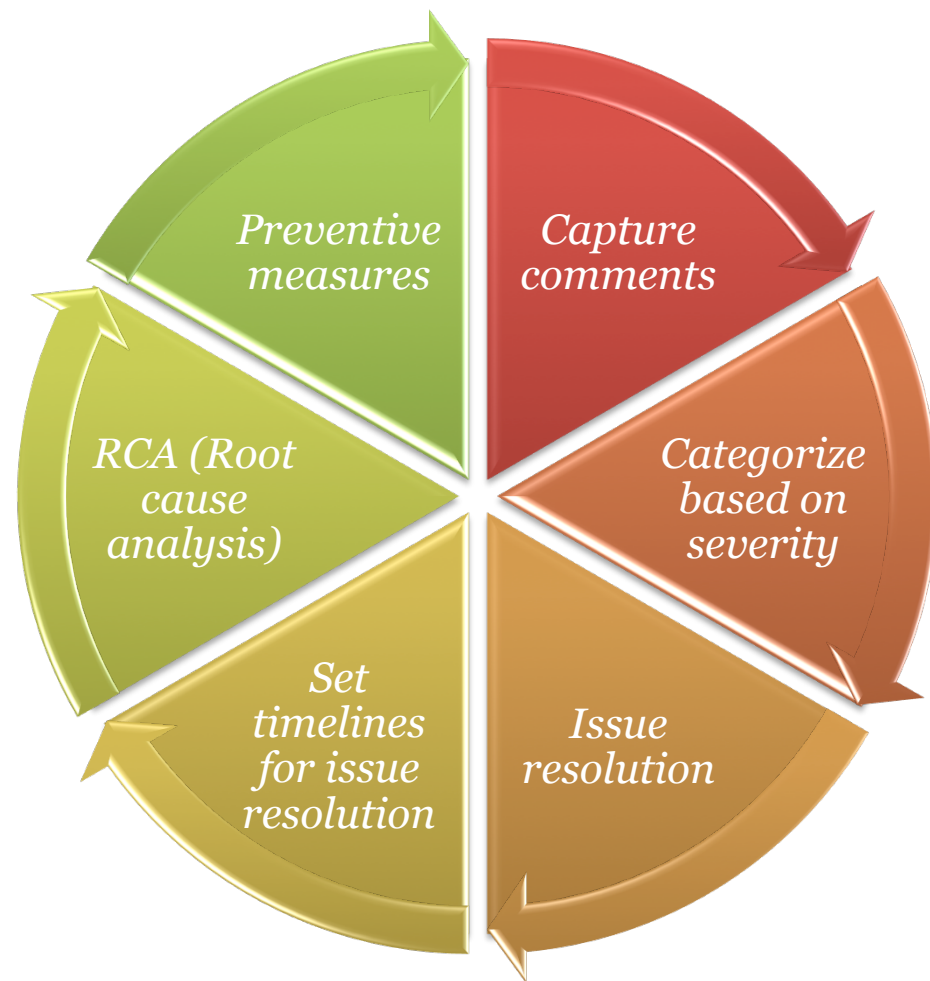
- Use numeric version of the variables instead of character where ever possible for conditional statements. (eg AEACN variable)
- Effective use of character function (index, strip, upcase, compbl, catx) to pick the right values
eg Race collected in multiple variables can be concatenated using CATX function
- Always use Data= in Proc statement

Content based Programming

- *Reviewing aCRF*
- *Reading SAP*
- *Understanding the data*

- *Makes work more interesting*
- *Keeps the programmer more alert and engaged*

Measure, Analyze & Improve

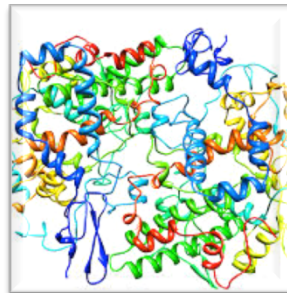


Accountability & Ownership



*Ownership of
output*

*Communication
is the key*



*Increasing
complexity of
Study Designs*

Importance of technology

Automation

- *Creation of macro libraries*
- *Reporting tools*
 - *Pfizer's reporting tool CDARS*
 - *GSK's reporting tool HARP*



References

- *Data handling and reporting in clinical trials with SAS- Angello Tinazzi*
- <http://www.appliedclinicaltrials.com/do-it-right-the-first-time>
- *Reading and resolving OPENCDISC message- Penny Wang*
- *A SAS programmers guide to project and program level quality- Paul Gorell*
- *Quality control and senior biostatistical review plan – Silvia Geraci*
- *Training statistical programmers in SAP review skills- Sasha Ahrweiler*
- *Good programming practices in Healthcare – Gregory S Nelson & Jay Zzhou*
- *Good programming practices in healthcare, Gregory S Nelson & Jay Zhou*